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Case Report

Serotonin Syndrome Precipitated by Amantadine in a Patient With Persistent Post Concussive Symptoms — A Case Report

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Abstract Symptoms after mild traumatic brain injury (MTBI) can persist for greater than 1 month in up to 20% of individuals, yet there are no current medications approved by the Food and Drug Administration for treatment of specific concussion related sequelae. Amantadine, a dopamine agonist and N-Methyl-D-aspartate antagonist, is increasingly being used as a treatment option for individuals with traumatic brain injury across the spectrum of injury severity. This case report describes a 22-year-old individual who sustained an MTBI without loss of consciousness or post-traumatic amnesia after striking their head against a metal cabinet. The individual was referred to an interdisciplinary outpatient brain rehabilitation program secondary to persistent symptoms after MTBI, was prescribed amantadine for post-traumatic headache 97 days after injury, and subsequently developed symptoms of serotonin syndrome (SS) within 10 days of medication initiation. While SS caused by amantadine has been described in individuals with renal failure, this case report is the first to describe amantadine precipitating SS - confirmed by a validated diagnostic criterion and successfully treated with lorazepam and cyproheptadine - in a patient with normal renal function already on duloxetine, bupropion, and gabapentin. This case report is important in elucidating potential contributions of amantadine to the

List of abbreviations: ED, emergency department; MTBI, mild traumatic brain injury; SS, serotonin syndrome; TBI, traumatic brain injury.
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Off Label Use/Unapproved Drugs or Products: This manuscript discusses the use of amantadine in the treatment of brain injury. While this medication is used by clinicians and in standard of care in those with severe traumatic brain injury/disorders of consciousness, it is not Food and Drug Administration approved for treatment of symptoms of traumatic brain injury. The product is still investigational in this regard.
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development of SS and highlighting the important role clinicians have in assessing for polypharmacy when prescribing amantadine for individuals with traumatic and acquired brain injuries.

Mild traumatic brain injury (MTBI), defined as a traumatic external force to the head and/or body involving up to 30 minutes of loss of consciousness as well as up to 24 hours of post-traumatic amnesia,[1] makes up the vast majority of traumatic brain injury (TBI) of all severity.[2] Approximately 20% of individuals experience persistent symptoms greater than 1 month after MTBI.[3] An MTBI can affect multiple neurotransmitters including serotonergic systems involved in neurobehavioral functioning.[4] For individuals with chronic symptoms, pharmacologic treatment is recommended to be focused on primary symptom management including treatment of headaches, anxiety, and depression. Yet, there is no Food and Drug Administration currently approved medication specifically for treatment of either post-traumatic headache or the neurobehavioral sequelae after MTBI.[5]

While amantadine was initially used mainly for individual's with Parkinson's disease,[6] it is increasingly being used in the rehabilitation setting as a treatment option for recovery after TBI.[7,8] Though evidence is strongest for use to promote neurorecovery in individuals who have sustained a severe TBI,[9,10] it has also been studied in patients with MTBI as a treatment option for post-traumatic headache as well as for overall symptom improvement.[7,11] In addition to its use for individuals with TBI, amantadine is also increasingly being trialed within the rehabilitation setting as a treatment option for individuals with other acquired brain injuries, though evidence remains limited.[12]

As amantadine is becoming more commonly prescribed in neurorehabilitation, an understanding of its neuropharmacology and side effect profile is important to treat individuals safely and effectively after TBI. Side effects after amantadine are most commonly associated with individuals with renal failure and are related primarily to those mediated by dopaminergic and glutaminergic activity.[13] The aim of this report is to describe a patient with normal renal function already on multiple medications affecting serotonin levels, who developed serotonin syndrome (SS) after initiating treatment with amantadine, and elucidate the potential contributions of amantadine to the development of SS in this individual.

Case description

A 22-year-old non-binary adult with a past medical history of major depressive disorder, anxiety disorder, migraine headache, asthma, as well as 3 prior MTBIs without loss of consciousness (age 4, age 11, age 19), struck their head against a metal cabinet after picking up something off the ground. There was no loss of consciousness reported, though an immediate onset of headache and dizziness was described. They initially presented to an urgent care center and, because of persistent symptoms, then presented to the emergency department (ED), where they were discharged home. Medications at time of injury included duloxetine 40 mg twice a day and bupropion 300 mg daily.

A timeline of key dates can be seen in table 1. The patient presented to their primary care physician with ongoing headache, nausea, decreased appetite, dizziness, light sensitivity, sound sensitivity, fatigue, and difficulty with thought process/finding words. Head Computed Tomography done at that time was within normal limits. The patient was prescribed 20 tablets of ondansetron 9 days after injury, and gabapentin was started for headache relief at 100 mg 3 times a day. The patient was seen by an Occupational Therapist, who noted patient was able to accomplish basic activities of

Table 1 Timeline of events

Date	Description
12/29/2021	MTBI sustained with immediate onset of headache and dizziness. Patient taking bupropion 300 mg and duloxetine 40 mg twice a day at time of MTBI.
1/12/2022	Gabapentin started for headaches 100 mg three times a day
2/10/2022	Gabapentin dose increased to 300 mg three times a day
3/1/2022	Bupropion increased from 300 mg to 450 mg
3/8/2022	Botulinum toxin started for post-traumatic headache with migraine phenotype
3/29/2022	Seen in outpatient specialty brain rehabilitation clinic for persistent symptoms
4/5/2022	Amantadine prescription filled
4/15/2022	Patient noticed tremor
4/24/2022	Admitted to acute hospital with worsening tremor, bilateral ankle clonus, ocular clonus, tachycardia
4/24/2022	Received cyproheptadine and lorazepam
4/28/2022	Discharged from hospital
5/23/2022	Follow-up in outpatient rehabilitation clinic

Abbreviations: MTBI = mild traumatic brain injury.

daily living, though otherwise had limited activity tolerance. Because of the patient's post-traumatic headache in the context of a prior diagnosis of migraine headache, a referral to Neurology was placed. Neurology recommended a trial of botulinum toxin injections, and gabapentin was also increased to 300 mg 3 times daily. Four weeks after gabapentin dose increase, bupropion was further increased from 300 mg to 450 mg secondary to complaints of worsening mood.

The patient was subsequently referred to a specialized interdisciplinary outpatient brain rehabilitation program and was seen by a physiatrist. A primary concern at that time was headache and patient reported minimal relief with gabapentin. Neurological examination was normal. They had not been taking ondansetron for several months by that point and had been on the increased dose of bupropion 450 mg for 35 days as well as the increased dose of gabapentin for 54 days. The dose of duloxetine remained the same as prior to injury. Amantadine 100 mg twice daily was initiated for treatment of post-traumatic headache based on prior research showing a benefit of amantadine in individuals with post-traumatic headache after MTBI,[7] and gabapentin taper was begun per patient request secondary to lack of efficacy. Ten days after beginning amantadine, the patient reported a substantial improvement with headache. They also described a new onset of tremor which was thought to be potentially related to a lower dose of gabapentin, and patient was recommended to increase the gabapentin dose from 200 mg back to 300 mg 3 times daily. The tremor continued to worsen over the next several days and they subsequently presented to the ED. On presenting to the ED, the patient confirmed taking the following medications: duloxetine 40 mg twice daily, bupropion 450 mg daily, gabapentin 300 mg 3 times daily, and amantadine 100 mg twice daily. In the ED, the patient was found to have substantial tremor, bilateral spontaneous and constant ankle clonus, inducible upper extremity clonus, ocular clonus, and tachycardia, which met criteria for SS by Hunter Criteria. Lab testing including electrolytes, renal function, hepatic function, creatine kinase, and complete blood counts were all normal, and urine drug screen was negative. Head CT was obtained and was within normal limits. They were admitted in the intensive care unit for further management and were initially treated with 12 mg cyproheptadine and 1 mg lorazepam. They were given cyproheptadine 2 mg every 2 hours, and received a total dose of 24 mg before it was discontinued the following morning. The patient's symptoms relating to SS resolved within 24 hours of receiving cyproheptadine and lorazepam. Initially, all their centrally acting medications were held upon admission to the hospital, and the patient was subsequently restarted on duloxetine at a lower dose of 40 mg daily. Amantadine and bupropion were discontinued upon hospital discharge.

The patient followed up several weeks later in the outpatient interdisciplinary rehabilitation specialty clinic. At that time, they had discontinued both amantadine and bupropion, and continued duloxetine 40 mg daily. The patient reported improvement in symptoms of dizziness and memory, though headaches and fatigue persisted. The patient continued to follow-up with Neurology for botulinum toxin injections, with documentation of improvement in overall symptoms including persistent headache since the MTBI.

Ethics information and reporting guidelines

This study conforms to all Case Report guidelines regarding the CARE checklist (for CAse REports) for this case report (see supplemental checklist).[14] Consent was obtained from the patient to present this Case Report.

Discussion

This case describes the first report of a patient with otherwise normal renal function who developed SS precipitated by amantadine. A strength of this case report is that SS diagnosed in this patient met nearly all criteria the Hunter Criteria, which has a sensitivity of 84% and specificity of 97% in diagnosing SS (table 2).[15] Hunter Criteria also requires a person to be on a serotonergic agent, which was met as the patient had been on duloxetine. Their rapid clinical improvement after receiving cyproheptadine, a histamine-1 receptor antagonist with serotonin antagonist properties that is recommended to be administered at an initial dose of 12 mg then 2 mg every 2 hours until symptoms improve, further supports this diagnosis.[16,17] Neuroleptic Malignant Syndrome and anticholinergic toxicity were ruled out based on the presence of spontaneous myoclonus, absence of fever, normal creatine kinase, normal leukocytes, and no exposure to neuroleptic agents nor strong anticholinergic agents.[18]

Baseline increased serotonin levels in this individual were predominantly related to the interaction of multiple medications that this patient was taking. Bupropion primarily influences dopamine receptors, though as a strong CYP2D6 inhibitor, it can increase the concentration of duloxetine in the serum.[19] Duloxetine has both norepinephrine and direct serotonin reuptake inhibitory activity, thus an increase in duloxetine concentration is expected to increase serotonin levels and has been found to directly cause SS.[20] Given that the patient had been on the same dose of duloxetine since injury with the same dose of bupropion for over 6 weeks prior to the onset of any symptoms related to SS, this interaction is unlikely to have been a primary direct cause of SS. The case reports of bupropion-associated SS are primarily related to bupropion overdose or a combination of bupropion with other serotonergic agents,[21-25] and cases of SS involving bupropion have predominantly been reported

Table 2 Hunter Criteria

Requires a patient to be on a serotonergic agent and have at least 1 of the following present:

1) Spontaneous clonus
2) Inducible clonus AND diaphoresis or agitation
3) Ocular clonus AND diaphoresis or agitation
4) Tremor AND hyperreflexia
5) Temperature above 38 °C AND ocular or inducible clonus

acutely after a medication change/adjustment,[22] with only 1 study demonstrating SS occurring after 3 weeks.[23] The possibility that the duloxetine/bupropion combination solely contributed to SS in this patient cannot be completely ruled out; however, given a case series of 14 individuals who developed SS at a mean of 6 weeks post medication changes, though none of which involved bupropion or duloxetine.[26] In addition, gabapentin has been found to increase serotonin levels[27] and has been implicated in causing SS as well,[28] the patient had been on the same dose of this medication for 9 weeks prior to SS. Lastly, ondansetron has been found to be implicated in developing SS,[22,29] though the patient had only been prescribed this medication for 20 tablets 9 days after injury, had not refilled the medication, and denied taking the medication several months before starting amantadine, thus ondansetron is unlikely to have contributed to SS.

Taken as a whole, the patient was already at a considerable risk of SS based on the interaction of the high dose of duloxetine and bupropion, along with gabapentin. With the combination of all these medications, any slight increase in serotonin level or change in the receptor sensitivity could have triggered SS in this individual. Overall, symptoms of SS in this individual started 10 days after initiating amantadine, and without other new medication during the period leading up to symptoms, this suggests that amantadine played a role in precipitating SS. The precise mechanism of the amantadine interaction in this case remains unclear, although several mechanisms might be plausible. While amantadine is primarily a dopamine agonist and N-Methyl-D-aspartate antagonist, it has been reported to cause SS in patients with renal failure or in individuals concomitantly taking amantadine with other medications that have serotonergic activity.[13,30] Amantadine does not seem to have direct serotonergic activity since the symptoms in this case report started 8 days after beginning amantadine, while most SS cases typically happen between 6 and 48 hours when there is a direct increase in serotonergic activity.[31] An animal model showed that when amantadine was combined with other serotonergic agents, this resulted in levels of serotonin that were increased as compared with administration of an antidepressant alone.[32] In this study, antidepressant medications administered with amantadine elicited a gradual increase in serotonin which became significant after 14 days, which is comparable with the patient reported in this case report who presented to the ED 18 days beginning amantadine initiation. While the interaction was felt to be related to N-Methyl-D-aspartate receptor antagonists potentiating the effect of antidepressants with regard to increased extracellular serotonin, the precise mechanism was reported as unclear.[32] Ultimately, a limitation of this case study is that the precise mechanism of amantadine's role in precipitating SS is unclear, and further research is needed to understand this.

Although the mechanism of how amantadine contributed to SS is uncertain, this case is important for clinicians taking care of individuals with traumatic and acquired brain injuries as a clear example of the potential deleterious effects of polypharmacy. After discontinuation of both amantadine and bupropion, as well as lowering the dose of duloxetine, the patient reported improvement in many symptoms that had been attributed to their persistent post concussive symptoms. Although the effects of natural recovery several months after MTBI is possible, the overall chronicity of symptoms with improvement only after discontinuing several centrally acting medications suggests that there may have been an iatrogenic component to ongoing symptoms after MTBI relating to polypharmacy in this individual.

Conclusions

This is the first case report describing amantadine contributing to the development of SS confirmed by Hunter Criteria in a patient with normal renal function and on multiple medications affecting serotonin. This case highlights the importance of a careful review of medications and their interactions when recommending pharmacologic treatments in the neurorehabilitation setting.

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